Nutritional Influences on Metal Toxicity: Cadmium as a Model Toxic Element

by M. R. Spivey Fox*

The nutrient quality of the diet has been shown repeatedly to be a significant factor in modifying the response of man and animals to toxic element exposure. Deficiencies of several essential nutrients have been shown to exacerbate the effects of cadmium and supplements of such nutrients have been shown to ameliorate the toxicity. Thus the effects of exposure to a toxic element, such as cadmium, may vary, depending on interactions with other elements which are present in the diet in different concentrations.

Introduction

It is becoming increasingly recognized that the composition of a person's diet is an important determinant in resistance to many adverse factors, including excessive metal intake. The possibility that dietary intake of certain heavy metals for which no function is known could cause imbalances of essential trace minerals in the general population was recognized by the Food and Nutrition Board in the eighth edition of Recommended Dietary Allowances published in 1974 (*1*). Consumption of a balanced and varied diet was recommended to minimize such imbalances. Today a wide variety of nutrient supplements recommended for overcoming environmental stresses are being marketed by companies responsible for these claims. Regulation of these supplements is complex. Except for children under 4 years of age and pregnant and lactating women, current legal restraints prevent the Food and Drug Administration from restricting nutrient supplements to levels that are nutritionally valid (*2*), and determinants of regulatory action are based solely on considerations of safety. It is important, therefore, to evaluate present levels of metal exposure and the quantities of dietary nutrients that might either augment or protect against adverse effects of the metals so that the multifaceted components contributing to safety can be intelligently incorporated into regulatory decisions.

Cadmium is an environmentally important toxic

metal that has been studied extensively with respect to essential nutrients. The information available for cadmium is useful in evaluating not only its adverse effects, but for establishing a model for planning studies relative to the adverse effects of other toxic elements about which less is known.

The effects of cadmium have been extensively reviewed (*3–10*). The relationship between dietary nutrient intake and the effects of cadmium has been reviewed (*11–13*), as well as factors pertinent to evaluating dietary cadmium intake by man (*14*).

An Overview of Cadmium Problems in Man

Human beings exposed to unusually high levels of cadmium, either industrially or via polluted food and water, typically develop a mild anemia, enteropathy, damaged renal tubules, and osteoporosis. The latter was extremely severe and very painful in the Japanese women who developed Itai-itai Byo. There are limited data showing that some cadmium-exposed workers had an increased incidence of prostate cancer. The effect of cadmium on hypertension and other cardiovascular diseases remains controversial. It appears that the greatest hazard to the general population from increasing cadmium exposure is kidney damage. There is considerable evidence that when the cadmium content of the renal cortex reaches 200 ppm, cadmium is lost from the kidney via the urine, and renal tubular damage results (*5*). The biological half-life of cadmium in the human kidney has been estimated to be 18 to 33 years or longer (*7, 15, 16*).

* Division of Nutrition, Food and Drug Administration, Washington, D. C. 20204.

The typical dietary intake of cadmium in the United States has been estimated to be approximately 50 μg/day for adults (17, 18). The Food and Drug Administration monitors the levels of cadmium in the United States diet, based on analyses of 12 classes of foods. Mahaffey et al. (17) have recently summarized some of these data. Food classes that were important sources of cadmium had concentrations as follows: dairy products, 0.005 ppm; meat, fish, and poultry, 0.0093 ppm; grains and cereal products, 0.028 ppm; potatoes, 0.046 ppm; leafy vegetables, 0.051 ppm; legume vegetables, 0.006 ppm; root vegetables, 0.021 ppm; garden fruits, 0.019 ppm; fruits, 0.042 ppm; oils, fats, and shortenings, 0.027 ppm; sugars and adjuncts, 0.0083 ppm; beverages, 0.0057 ppm. Based on consumption, the major food groups contributing cadmium as percent of the total daily intake were as follows: meat, fish, and poultry, 4.9%; dairy products, 7.7%; beverages, 12.7%; potatoes, 17.8%; fruits, 18.3%; grains and cereals, 22.8%.

A few foods contain unusually high concentrations of cadmium. These are liver, kidney, and most of the bivalves, such as oysters, depending on their exposure to cadmium. The diet composites of the Food and Drug Administration contain liver and liver products, but not kidney or oysters.

When single meals of kidney homogenate were extrinsically labeled with cadmium-115m (approximately 110 μg total cadmium) and consumed by five men, the absorption of cadmium was approximately 6%, based on retention after the rapid turnover pools were lost from the body (19). McLellan et al. (20) gave 14 fasting healthy subjects a meal of rolled oats and milk followed immediately by $^{115m}CdCl_2$ and $^{51}CrCl_3$ in deionized water. The total cadmium intake was 22–29 μg by analysis. The average ^{115m}Cd retention after clearance of the rapidly lost cadmium pools and 14 days after the disappearance of the ^{51}Cr was 4.6%, with a range of 0.7–15.6%. In man, as in animals, urinary and intestinal losses of absorbed cadmium are small and no safe way is known to remove cadmium from the kidney. The kinetics of cadmium turnover in man have been discussed in detail by Friberg et al. (7).

Current estimates suggest that ingestion of 248–352 μg cadmium from food per day would lead to 200 ppm cadmium in the renal cortex by 50 years of age (7). Assuming that half the day's cadmium intake came from 300 g of a basic foodstuff, it was calculated that concentrations of 0.41–0.59 ppm (wet weight) in the food would have the same effect. The validity of these estimates has recently been demonstrated in Japanese women who consumed cadmium-polluted rice for many years (21). Duration and level of dietary cadmium intake and urine and blood cadmium levels were related to the level of urinary β_2-microglobulins, an index of renal tubular damage. Similar results have been found for both men and women 50 years of age or more (22).

A Joint FAO/WHO Expert Committee on Food Additives established provisional tolerable intakes of cadmium at 57-71 μg/day (23). These values, which are similar to present intake levels in the United States, offer approximately a 3.5-6 fold level of protection against cadmium accumulation to 200 ppm in the renal cortex by 50 years of age, based on the calculations of Friberg et al. (7). Because the provisional tolerable intake levels recommended by the FAO/WHO committee coincide with the level in the United States food supply, it is considered very important that the cadmium concentration in foods not be permitted to increase.

Effects of Dietary Nutrients in Increasing Risks from Cadmium

Young experimental animals fed high levels of soluble cadmium salts, 5 ppm cadmium or more, have typically failed to grow normally and developed anemia, poorly mineralized bones, enteropathy, renal tubular damage, and sometimes hypertension (11–13). High levels of dietary cadmium have led to decreased tissue levels of zinc, iron, copper, and calcium in the bones, although the concentrations of zinc and copper in the kidney sometimes were increased. There is considerable evidence that cadmium interferes with absorption of zinc, iron, copper, and calcium.

The current levels of cadmium present in the human diets would not be expected to influence the absorption or metabolism of these essential nutrients. Rather, these high-level cadmium studies in animals have identified the most sensitive cadmium-essential element antagonisms and suggest that deficiencies of these elements could lower the threshold for absorption and foster the long-term toxic effects of cadmium. It is also possible that at low levels of cadmium intake, interactions in processes other than absorption become principally important because of differences in metallo-complex formation and biological turnover.

Signs of zinc deficiency were exacerbated by additions of 2 ppm cadmium to the diet of poults (24), 20 ppm cadmium to the diet of chicks (25), and 3.4 ppm cadmium to the drinking water of rats (26). A 7-day period of low zinc intake by young Japanese quail increased the amount of cadmium in the liver as compared with that in control birds receiving the required amount of zinc (27). The level of dietary cadmium in this study was 0.145 ppm, about 50%

higher than the equivalent level of cadmium in human diets.

Hill et al. (28) found that the signs of copper and iron deficiencies were more marked when 25–400 ppm cadmium was fed to chicks. Copper-deficient rats and mice were more severely affected by 100 ppm cadmium than were controls (29). Campbell and Mills (30) found that when they fed rats a diet containing required levels only of zinc and copper, as little as 1.5 ppm dietary cadmium caused a decrease in serum ceruloplasmin.

Flanagan et al. (31) observed impaired growth and accentuated development of anemia when 1.12 ppm cadmium was added to the drinking water of mice receiving a low-iron diet. A tracer of $^{109}CdCl_2$ was also present in the drinking water until 6 days prior to the termination of the 16-week experiment. Water intake was the same for the two groups. Iron deficiency produced marked increases in the cadmium content of the duodenal mucosa, the transfer of cadmium past the intestinal mucosa into the body, and the proportion of this cadmium that was deposited in the kidneys. Total amounts of cadmium were greater in the stomach, duodenum, cecum, liver, and kidneys of iron-deficient as compared with iron-sufficient mice. The cadmium in liver and kidneys was bound primarily to large proteins rather than metallothionein, possibly because cadmium intake was too low to induce synthesis of metallothionein. These studies confirm and expand earlier work from the same laboratory on the effect of iron deficiency in producing higher cadmium absorption from an intragastric dose or greater mucosal uptake of cadmium in iron-deficient mice during open-ended duodenal perfusion (32, 33). Ragan (34) reported that iron-deficient rats retained more of a single intragastric dose of ^{109}Cd citrate (9.9 μg cadmium) than did controls 48 hr after dosing. The iron-deficient rats retained significantly more of the dose in the liver, femur, blood, marrow, and muscle.

Flanagan et al. (31) also administered $^{115m}CdCl_2$ (25 μg cadmium) and $^{51}CrCl_3$ marker in a breakfast of rolled oats and milk to fasting human volunteers (12 females and 10 males). The women absorbed significantly more cadmium (7.5 vs. 2.6% of the dose) than the men. The mean serum ferritin values (17 vs. 40 ng/ml) and hemoglobin (14 vs. 16 g/dl) were significantly lower for the women. Cadmium absorption was inversely proportional to serum ferritin concentration when data from both men and women were considered together; the correlation coefficient for cadmium absorption values versus the logarithm of serum ferritin values was 0.68.

The severe bone demineralization that occurred in patients with Itai-itai Byo and their low calcium intake led to several studies on relationships between calcium and cadmium. Increased levels of cadmium in liver and kidney were found by Larsson and Piscator (35) in adult rats fed a calcium-deficient diet and 25 ppm cadmium in the drinking water. Feeding 200 ppm cadmium in a calcium-deficient diet to rats during pregnancy caused a 3.8-fold increase of cadmium in tissues of the dams and an 8.6-fold increase in the pups (36). Higher concentrations of cadmium were found in the kidney, liver, and lung of growing male rats fed a calcium-deficient diet and 25 ppm cadmium in the drinking water as compared with rats receiving adequate calcium (37). Young adult female rats had higher concentrations of cadmium in the femur and kidney when they were fed 100 ppm cadmium in a diet deficient in calcium as compared with an adequate calcium-supplemented diet (38). The experiments lasted 60 days. With low calcium intake, there was an increase in cadmium in liver and kidney of mice fed cadmium in the form of high cadmium rice (39).

In the above studies, high levels of cadmium were fed either in the diet or the drinking water. A tracer dose of carrier-free ^{109}Cd was also found by Washko and Cousins (40) to accumulate in greater amounts in the intestinal mucosa, serum, lungs, liver, kidney, and urine of rats fed a low calcium diet as compared with a normal calcium diet. Hamilton and Smith (41) pair-fed rats a calcium-supplemented diet to equal food intake of rats fed a low calcium diet. An oral dose of ^{115m}Cd (11.2 μg total cadmium) was administered at 7 days. After 10 days, the cadmium in the liver was higher for calcium-fed rats and cadmium in the kidneys was higher in the calcium deficient rats. The total amount of cadmium in the two organs was the same for the two groups. The retention of cadmium by the small intestine by 10 days was greater for the calcium-deficient rats.

Fowler et al. (42) found morphological changes in renal arteries and capillaries and deposition of peritubular connective tissue fibers in rats receiving cadmium (0.2, 2, 20, and 200 ppm cadmium in the drinking water). These changes were dose-related. In this study higher concentrations of cadmium were found in the kidneys of the rats receiving a low-calcium diet as compared with a normal calcium diet. Severe morphological changes in the kidneys and bones were reported by Itokawa et al. (43) for rats fed a low calcium diet and 50 ppm cadmium in the drinking water. Marked spinal curvature was observed in rats fed 20 ppm cadmium in a diet low in calcium, zinc, and protein (44).

The uptake by liver and kidney of a tracer dose of ^{109}Cd was shown by Cousins and Feldman (45) to be unaffected by pretreating vitamin D-

deficient chicks with the vitamin. After oral dosing with ^{109}Cd, the birds were fasted for 24 hr and killed, and the radioactivity was measured. The calcium level of the serum was depressed in deficient birds and it was increased by the vitamin D dose. The design of this study did not include evaluation of the effects of intestinal absoption of calcium on cadmium absorption.

A marked increase in absorption of cadmium was produced by feeding a low protein diet to mice for 24 hr before and 24 hr after an oral dose of ^{115m}Cd (46). When 200 ppm cadmium was added to a diet low in protein, calcium, phosphorus, and fiber, young rats grew slowly (47). Marked depilation resulted from abnormal biting and eating of hair from other rats in the same cage. Removal of cadmium reversed these effects.

Effects of Dietary Nutrients in Decreasing Risks from Cadmium

Numerous studies have demonstrated that toxic effects of injected cadmium may be lessened by injections of other elements. These studies, which have varying degrees of relevance to dietary effects, have been summarized in the reviews cited at the beginning of this paper.

In 1961, it was shown by Supplee (24) that supplements of zinc in excess of the young turkey's requirement decreased the hock and feather abnormalities produced by 80 ppm dietary cadmium. A supplement of 75 ppm zinc caused a small increase in the hematocrit of severely anemic Japanese quail fed 75 ppm cadmium (48). The cadmium concentration in the liver of young Japanese quail fed 0.145 ppm cadmium with a tracer of ^{109}CdCl$_2$ was less when the zinc content of the diet was increased from 30 ppm (requirement) to 60 ppm (27, 49).

Very high levels of cadmium have been shown to produce anemia in several species. A supplement of 400 ppm iron as ferrous sulfate had a marked effect in preventing the low hemoglobin level produced in rats by 100 ppm cadmium (50). Similar beneficial effects were reported for dietary supplements of iron(II) and injected iron-dextran in rats fed diets with 100 ppm cadmium and in pigs receiving 154 ppm cadmium (51, 52). Iron(II) as ferrous sulfate was markedly more protective than iron(III) as ferric citrate in preventing growth depression and anemia produced by 75 ppm dietary cadmium in young Japanese quail (48).

Mice given 10, 20, or 40 ppm cadmium in drinking water during pregnancy produced normal numbers of fetuses; however, fetal size was decreased in proportion to cadmium dose (53). Maternal weight gain with 40 ppm cadmium was decreased during the last 4 days of gestation although food intake was not significantly affected. Mild anemia was observed in the pregnant females, whereas anemia in the young was very severe. Injection of 1 mg iron as iron-dextran on days 1 and 14 of pregnancy prevented the adverse effects of 40 ppm cadmium. These data support the conclusion that levels of cadmium having little or no apparent effect on pregnant females reduced their iron stores, so that either little iron was available to transport to the fetuses or else cadmium may have decreased the transfer of iron across the placenta.

High levels of cadmium (25 to 400 ppm) fed to chicks in a diet deficient in copper and iron caused mortality, reduced growth, and caused anemia and atony and elongation of the gizzard (28). Zinc supplements improved growth rate and prevented the gizzard abnormality. Copper supplements decreased mortality and iron supplements decreased mortality and improved growth.

Supplemental copper increased the hematocrit of anemic Japanese quail fed 75 ppm cadmium (48). Individual supplements of chromium, cobalt, selenium, nickel, molybdenum, and pteroylglutamic acid did not affect either hematocrit or body weight. A supplement of L-cysteine · HCl (0.1% of the diet) had a small effect on increasing hematocrit and body weight; the latter was observed in only one of two experiments.

Simultaneously doubling the required levels of zinc, manganese, and copper in a soy isolate diet was shown by Jacobs et al. (54) to influence markedly the metabolism of 0.062, 0.125, 0.25, 0.50, and 1.00 ppm dietary cadmium fed to young Japanese quail for 1 week with a tracer of ^{109}CdCl$_2$. Cadmium accumulated in the duodenum, liver, and kidneys in a linear log-dose, log-response relationship. The supplemented birds had less cadmium in the liver, kidneys, and whole body, whereas the concentration in the duodenum was not affected. Cadmium concentration in the jejunal-ileal section of the small intestine was decreased by the supplement. These dietary concentrations of cadmium bracketed the dietary concentrations of cadmium equivalent to the intake of man (approximately 0.08–0.1 ppm) when calculated to a dry, fiber-free diet of the type fed in this experiment. These relatively modest increments of zinc, manganese, and copper suggest that long-term effects of cadmium uptake may be significantly influenced by dietary mineral levels.

Similar protective effects of the same supplement were observed by Jacobs et al. (55) in young Japanese quail fed 1 ppm cadmium and a tracer of ^{115m}CdCl$_2$ for 1 week. The birds continued to receive the same diets without ^{115m}Cd for 50 days. The slope

of the long-term whole body retention curve showed a beneficial effect of the supplement in accelerating the loss of cadmium. This effect was less than that on absorption, which was observed in the short-term experiment (54), but it is still important when we consider the very long biological half-life of cadmium in the human kidney.

Ascorbic acid has been found to protect markedly against the anemia and growth depression produced in young Japanese quail receiving 75 ppm cadmium in the diet (56). The minimal effective level was approximately 0.05%, which is approximately two and one half times the guinea pig's requirement or equivalent to a daily intake of approximately 780 mg per day by man. Cadmium did not affect the total ascorbate content of the liver (48). D-Isoascorbic acid also protected against anemia and growth depression, and both forms protected against the poor bone mineralization caused by cadmium. Removal of ethoxyquin from the diet had no effect. It appears that the primary effect of ascorbic acid was to improve iron absorption; however, injected ascorbic acid produced a small improvement in hematocrit. The effect of ascorbic acid on cadmium concentration in the liver and kidneys was variable; however, decreased levels of cadmium were observed in a few experiments with supplements of ascorbic acid and iron (100 ppm iron as ferrous sulfate).

Pathological changes produced by 75 ppm cadmium in the young Japanese quail included testicular hypoplasia, bone marrow hyperplasia, immature circulating erythrocytes with small amounts of basophilic cytoplasm surrounding the nucleus, hypertrophy of both ventricles, enteropathy with clusters of mucin-filled goblet cells at the villous tips, decreased granulation of adrenal medullary cells, and increased periodic acid-Schiff reactivity of esophageal mucus glands (57). Supplements of ascorbic acid markedly decreased or prevented all of these changes.

Male and female rats were fed either 50 or 75 ppm cadmium with or without a combined supplement of 1% ascorbic acid and 400 ppm iron as ferrous sulfate (58). Cadmium caused reduced growth rate, lowered hemoglobin and hematocrit, and hypertrophy of the duodenum. The combined supplement was markedly protective against all of these toxic effects and also caused reduced tissue concentrations of cadmium.

Diets deficient in pyridoxine or containing high levels (22 and 44 ppm pyridoxine) of the vitamin were fed to rats receiving 100 ppm cadmium in the diet (59). In the absence of cadmium, pyridoxine deficiency did not affect hematocrit but markedly reduced growth rate. Cadmium decreased the growth rate of all rats compared with their controls.

At 6 weeks, when body weights of all rats were similar except for pyridoxine-deficient groups, the hematocrit values for pyridoxine- and cadmium-fed groups were similar and markedly lower than the controls. By 12 weeks, the hematocrit values of rats fed 22 ppm pyridoxine with cadmium were markedly higher than those of rats fed 44 ppm pyridoxine with cadmium, although body weights were similar. Among the cadmium-fed rats, the concentrations of cadmium in the livers and kidneys of pyridoxine-supplemented rats were lower than those in the deficient group. Iron concentrations in the livers of all cadmium-fed rats were low. The required level of 7 ppm pyridoxine was not fed; however, if 22 ppm pyridoxine could be assumed to be a normal control, 44 ppm pyridoxine had an adverse effect on hematocrit of cadmium-fed rats at 12 weeks of age. It appears reasonable to interpret the relatively high hematocrit of the deficient rats fed cadmium as evidence of little dilution of initial iron stores associated with poor growth.

The type of dietary protein in purified diets was found by Fox et al. (60) to influence markedly the severity of cadmium toxicity. Japanese quail fed 75 ppm cadmium from 7 to 14 days of age became anemic, and had low amounts of liver iron, tibia zinc, and total ash when either casein and gelatin or soy isolate was the source of dietary protein. When dried egg white was the source of protein, cadmium either had no effect or a much lesser effect on these same measurements. The beneficial effects of dried egg white were attributed to better utilization of dietary iron and zinc. It has been suggested that the selenium content of the egg white may have influenced its beneficial effect (12); however, selenium was ineffective when added to the soy protein diet containing cadmium (48).

Effects of Age on Cadmium Uptake

The placenta is known to be an effective barrier against cadmium transport into the fetus. Henke et al. (61) proposed that by 3 years of age the child has accumulated almost one-third of the lifetime burden of cadmium. Kello and Kostial (62) found that in rats given a single oral dose of $^{115m}CdCl_2$ with milk and stock diets at 3, 6, and 52 weeks of age, retention of cadmium was significantly greater by the younger rats fed each type of diet. The greatest whole body retention at 6 days was 26.6% for rats that received cadmium at 1 week of age. Retention values for rats dosed at 3 and 52 weeks of age were 15.8 and 5.6% for the milk diet and 0.89 and 0.32% for the stock diet, respectively. Retention of in-

jected cadmium was not influenced by age or diet.

Sasser and Jarboe (63) dosed rats orally with $^{115m}CdCl_2$ 1 and 24 hr after birth. One day after dosing, the cadmium transported past the gastrointestinal tract was 7.9% of the dose for rats dosed 1 hr after birth and 1.4% for rats dosed at 24 hr, whereas the values were 12 and 5.4%, respectively, for rats killed 21 days after dosing. Cadmium was retained tenaciously for 15 days by the gastrointestinal tract of rats dosed either 2 or 24 hr after birth. ^{115m}Cd administered to 6-week-old rats was absorbed past the gastrointestinal tract by only 0.6%, 4 days after dosing.

Enteropathy Caused by Dietary Cadmium

Enteropathy was found in Japanese women who died from Itai-itai Byo (64). Ulceration of the stomach, small intestine (65), and colon (66) has been reported in rats given cadmium and necrosis of jejunal villi tips was observed in rabbits (67). Enteropathy in Japanese quail fed 75 ppm cadmium for 4 or 6 weeks has been studied extensively by Richardson and co-workers (57, 68). The small intestinal wall was dilated and thin, the villi were shortened and blunt, and the microvilli of absorptive and goblet cells were shortened. Clusters of goblet cells were observed near the villous tips. The gross, microscopic, and ultrastructural lesions resembled those occurring in human malabsorption syndromes, celiac disease, and tropical and nontropical sprue. Large, irregular electron-dense bodies were observed in the endothelium of the large veins. There was degeneration of some of the nerve plexuses in the muscularis propria. More recently, Mason et al. (69) showed that exposure of Japanese quail to only 1 ppm dietary cadmium between 12 and 14 days of age accelerated degeneration of absorptive cells at the villous tips in all birds. Continuous exposure from hatching to 14 days caused similar changes in about half of the birds.

Valberg et al. (70) found that the ^{109}Cd-thionein from intestinal mucosal cells was taken up by the mucosal cells similar to $^{109}CdCl_2$; however, less of the cadmium from the cadmium-thionein was transported into the body. The cadmium-thionein caused extensive necrosis of absorptive cells during a 1-hr exposure of the intestinal mucosa. Under the same conditions, cadmium chloride caused minor abnormalities. Changes in the enzyme activity and distribution of several metals in the soluble fraction of the duodenal mucosa have been reported in rats receiving cadmium (71).

These studies illustrate the sensitivity of the intestinal mucosa to the cytotoxic effects of cadmium.

Physical alteration of the absorptive surface and biochemical changes may introduce factors that must be considered in extrapolation from studies of high level cadmium exposure to those at levels typical of current human intake.

Nutritional Intervention to Protect Against Excess Metal Intake by Man

An assessment of the need for nutritional intervention to protect against dietary exposure to a toxic metal must involve several factors. These include (1) exposure level to the toxic metal, (2) levels at which undesirable effects might occur in the normal individual, (3) physiological and nutritional factors that increase risk, and (4) dietary intake of essential nutrients by the population.

The Food and Drug Administration has a continuing program to monitor the levels of lead, cadmium, arsenic, mercury, zinc, and selenium in foods. Foods are collected periodically from representative areas of the country to provide an indication of food intake by a 15 to 20-year old male. A summary of heavy metal data relative to the older teenage male was reported by Mahaffey et al. (17). The 1973 daily intakes of total mercury, lead, and cadmium were 6.7, 14.1, and 72–90%, respectively, of the FAO/WHO provisional tolerable intakes for man (23).

The FAO/WHO recommendations with regard to mercury, lead, and cadmium are the only standards established to provide guidance regarding reasonably safe levels of intake. It is well recognized that all inorganic elements are toxic at elevated levels of intake. The minimal levels at which adverse effects appear are usually approximately 20 or more times the required intake of essential trace elements. Nutrient deficiences can lower this level to 2-3 times the requirement. Elements required in large amounts may become toxic before the intake is double the requirement. The very young, the pregnant, and the elderly represent groups most apt to be at risk from these excess levels.

Once the conclusion is reached that undesirably high intakes of a given element are unavoidable, consideration should be given to the use of appropriate nutritional supplements to decrease the hazard. The data with cadmium clearly show that deficient intakes of several essential nutrients increased the toxicity of cadmium. Increased absorption of small amounts of cadmium have been shown in a few instances. Conversely, supplements of several essential nutrients in excess of requirements have been shown to reduce cadmium toxicity in ex-

perimental animals.

Correction of nutrient deficiencies is of great importance and might be envisioned as being simple to accomplish. In practice, however, this can be exceedingly difficult due to differences in dietary intake, to varying degrees of deficiencies, and to incidence of genetically determined differences in absorption, metabolism, and storage of essential minerals. Some of the wide variations within population groups are described below.

The use of nutrient supplements in excess of requirements must be approached with even more caution. Numerous antagonisms and interactions between essential minerals themselves and between essential minerals and other nutrients continue to be recognized. Virtually nothing is known about dietary imbalances that may have an adverse effect on the function of the newly recognized essential elements, such as silicon, arsenic, and nickel. Some of our recent data illustrate the type of interaction problem that might arise with a nutrient supplement. Supplements of zinc and ascorbic acid have been shown to be very beneficial individually in counteracting the toxicity of cadmium. A combined supplement of these would seem to be useful; however, we have recently found that the combination is much more antagonistic to copper than either alone (72). With modest dietary excesses of copper, the sensitive antagonism was not observed; however, marginally low copper intakes by man are common.

There is considerable evidence to suggest that significant numbers of people in the United States consume diets that are less than adequate with respect to essential minerals and other nutrients. Data from the first Health and Nutrition Examination Survey (1971–72) revealed clinical signs indicative of deficiencies of thiamine, niacin, vitamin C, vitamin D, and vitamin A in significant percentages (5% or more) of some population groups (73). Evidence of calcium-phosphorus imbalance and of iodine deficiency and excess were also reported. Calculations of nutrient intake from single 24-hr dietary recalls taken during the same survey revealed inadequate mean intakes by several population groups of protein, iron, vitamin A, and vitamin C (74, 75). The standards used to evaluate adequacy of calcium and vitamin A intake were considerably lower than the recommended dietary allowances of the Food and Nutrition Board (1). Evidence of zinc deficiency in children has been reported by Hambidge and co-workers (76–78).

The quantities of essential minerals in the total diet study by the Food and Drug Administration are also determined. From the diets for the older teenage male adjusted to 2800 kcal/day the mineral levels in the diets, as mg/day and percent of the U. S. Recommended Daily Allowance (RDA) (2), were recently reported as follows: calcium 1145, 114%; copper 1.5, 75%; iron 17.8, 99%; iodine 0.538, 359%; magnesium 354, 88%; manganese 3.7, 74%; phosphorus 1709, 171%; selenium 0.100 mg; and zinc 13.8, 92%, respectively (79). A U. S. RDA for manganese has not been established; the value used was 5 mg/day. The foods were selected to represent a nutritionally adequate diet; however, copper, magnesium, and manganese were significantly low, whereas phosphorus and iodine were present in excess.

Analyses of self-selected diets have been shown values that were low in zinc, manganese, copper, and magnesium (80–85). Ranges in the daily intakes of minerals, which have been reported in a few studies, have been found to be rather wide. Some examples are as follow: calcium 0.13–1.60 g, phosphorus 0.41–1.66 g, and magnesium 57–240 mg (80); manganese 0.8–7.1 mg, copper 0.1–15 mg, and zinc 1.7–9.1 mg (82); and manganese 0.7–7.6 mg, copper 0.6–8.5 mg, and zinc 7.2–42.9 mg (84). The ranges in 6-day averages for individuals were as follows: copper 0.58–2.03 mg and zinc 5.94–12.09 mg (83). These data show that many daily intakes of these elements were markedly deficient and that others were quite high. The ranges for the individual 6-day means for copper and zinc show that individuals can have very low intakes of these elements over significant periods of time.

It is well recognized that many nutrient interactions involving minerals take place in the gastrointestinal tract prior to absorption. Examples are the effect of ascorbic acid in increasing iron absorption and the effect of calcium and phytate in reducing zinc absorption. It is obvious that analysis of a day's diet does not provide sufficient data for assessing the relative adequacy or excess of mineral intake.

The importance of designing experimental animal models to be more applicable to man has been addressed by Fox (86). Differentiations have not been made between the effects of long-term nutritional status and the simultaneous intake of nutrient and toxic metal in assessing the protective efficacy of the nutrient. Whereas our knowledge of an animal's response to almost overwhelming doses of toxic elements is extensive, very little is known about the absorptive, sequestering, and transport processes and the metabolic effects of very low levels of intake. Basic information relative to these processes is needed in future investigations of nutrient-metal interactions to guide regulatory actions that will be most appropriate to diminishing the problems of human beings.

REFERENCES

1. National Research Council. Recommended Dietary Allowances, 8th ed. National Academy of Sciences, Washington, D. C., 1974.
2. Schmidt, A. M. Part 80—Definitions and standards of identity for foods for special dietary uses. Part 125—Label statements concerning dietary properties of food purporting to be or represented for special dietary uses. Fed. Reg. 41: 46156 (1976).
3. Schroeder, H. A., and Balassa, J. J. Abnormal trace metals in man: cadmium. J. Chron. Dis. 14: 236 (1961).
4. Schroeder, H. A., Nason, A. P., Tipton, I. H., and Balassa, J. J. Essential trace metals in man: zinc. Relation to environmental cadmium. J. Chron. Dis. 20: 179 (1967).
5. Friberg, L., Piscator, M., and Nordberg, G. Cadmium in the Environment. CRC Press, Cleveland, 1971.
6. Vallee, B. L., and Ulmer, D. D. Biochemical effects of mercury, cadmium and lead. Ann. Rev. Biochem. 41: 91 (1972).
7. Friberg, L., Piscator, M., Nordberg, G. F., and Kjellstrom, T. Cadmium in the Environment, 2nd ed. CRC Press, Cleveland, 1974.
8. Fleischer, M., Sarotin, A. F., Fassett, D. W., Hammond, P., Shacklette, H. T., Nisbet, I. C. T., and Epstein, S. Environmental impact of cadmium: A review by the panel on hazardous trace substances. Environ. Health Perspect. 7: 253 (1974).
9. Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health. Criteria for a Recommended Standard-Occupational Exposure to Cadmium. HEW Pub. No. (NIOSH) 76-192, Washington, D. C., 1976.
10. Doyle, J. J. Effects of low levels of dietary cadmium in animals—a review. J. Environ. Qual. 6: 111 (1977).
11. Fox, M. R. S. Effect of essential minerals on cadmium toxicity. J. Food Sci. 39: 321 (1974).
12. Sandstead, H. H. Nutrient interactions with toxic elements. In: Advances in Modern Toxicology, Vol. 2. Toxicology of Trace Elements. R. A. Goyer and M A. Mehlman, Eds., Halsted Press, New York, 1977, p. 241.
13. Nordberg, G. F., Fowler, B. A., Friberg, L., Jernelöv, A., Nelson, N., Piscator, M., Sandstead, H. H., Vostal, J., and Vouk, V. B. Factors influencing metabolism and toxicity of metals. Environ. Health Perspect. 25: 3 (1978).
14. Fox, M. R. S. Cadmium metabolism—A review of aspects pertinent to evaluating dietary cadmium intake by man. In: Trace Elements in Human Health and Disease. Volume II, A. S. Prasad, Ed., Academic Press, New York, 1976, p. 401.
15. Kjellstrom, T. A mathematical model for the accumulation of cadmium in the human kidney cortex. Nord. Hyg. Tidskr. 53: 111 (1971).
16. Tsuchiya, K., and Sugita, M. A mathematical model for deriving the biological half-life of a chemical. Nord. Hyg. Tidskr. 53: 105 (1971).
17. Mahaffey, K. R., Corneliussen, P. E., Jelinek, C. F., and Fiorino, J. A. Heavy metal exposure from foods. Environ. Health Perspect. 12: 63 (1975).
18. Bureau of Foods. Compliance Program Evaluation, FY 1974. Heavy Metals in Foods Survey. Food and Drug Administration, Washington, D. C., 1975, p. 17.
19. Rahola, T., Aaron, R. K., and Miettinen, J. K. Half-time studies of mercury and cadmium by whole body counting. In: Assessment of Radioactive Contamination in Man, I.A.E.A., Vienna, 1972, p. 533.
20. McLellan, J. S., Flanagan, P. R., Chamberlain, M. J., and Valberg, L. S. Measurement of dietary cadmium absorption in humans. J. Toxicol. Environ. Health 4: 131 (1978).
21. Kjellstrom, T., Shiroishi, K., and Evrin, P.-E. Urinary β_2-microglobulin excretion among people exposed to cadmium in the general environment. An epidemiological study in cooperation between Japan and Sweden. Environ. Res. 13: 318 (1977).
22. Nogawa, K., Ishizaki, A., and Kawano, S. Statistical observations of the dose-response relationships of cadmium based on epidemiological studies in the Kakehashi River basin. Environ. Res. 15: 185 (1978).
23. FAO/WHO Expert Committee on Food Additives. Evaluation of certain food additives and the contaminants mercury, lead and cadmium. WHO Tech. Rep. Ser. No. 505: 20, 32 (1972).
24. Supplee, W. C. Production of zinc deficiency in turkey poults by dietary cadmium. Poultry Sci. 40: 827 (1961).
25. Supplee, W. C. Antagonistic relationship between dietary cadmium and zinc. Science 139: 119 (1963).
26. Petering, H. G., Johnson, M. A., and Stemmer, K. L. Studies of zinc metabolism in the rat. I. Dose response effects of cadmium. Arch. Environ. Health 23: 93 (1971).
27. Jacobs, R. M., Jones, A. O. L., Morra, M. N., and Fox, M. R. S. Zinc antagonism of cadmium. Fed. Proc. 37: 405 (1978).
28. Hill, C. H., Matrone, G., Payne, W. L., and Barber, C. W. In vivo interactions of cadmium with copper, zinc and iron. J. Nutr. 80: 227 (1963).
29. Bunn, C. R., and Matrone, G. In vivo interactions of cadmium, copper, zinc and iron in the mouse and rat. J. Nutr. 90: 395 (1966).
30. Campbell, J. K., and Mills, C. F. Effects of dietary cadmium and zinc on rats maintained on diets low in copper. Proc. Nutr. Soc. 33: 15A (1974).
31. Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, M. G., and Chamberlain, M. J. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 74: 841 (1978).
32. Hamilton, D. L., and Valberg, L. S. Relationship between cadmium and iron absorption. Am. J. Physiol. 227: 1033 (1974).
33. Valberg, L. S., Sorbie, J., and Hamilton, D. L. Gastrointestinal metabolism of cadmium in experimental iron deficiency. Am. J. Physiol. 231: 462 (1976).
34. Ragan, H. A. Effects of iron deficiency on the absorption and distribution of lead and cadmium in rats. J. Lab. Clin. Med. 90: 700 (1977).
35. Larsson, S.-E., and Piscator, M. Effect of cadmium on skeletal tissue in normal and calcium-deficient rats. Israel J. Med. Sci. 7: 495 (1971).
36. Pond, W. G., and Walker, E. F., Jr. Effect of dietary Ca and Cd level of pregnant rats on reproduction and on dam and progeny tissue mineral concentrations. Proc. Soc. Exptl. Biol. Med. 148: 665 (1975).
37. Washko, P. W., and Cousins, R. J. Role of dietary calcium and cadmium binding protein in cadmium toxicity in rats. J. Nutr. 107: 920 (1977).
38. Itokawa, Y., Nishino, K., Takashima, M., Nakata, T., Kaito, H., and Okamoto, E. Renal and skeletal lesions in experimental cadmium poisoning. Histology and renal function. Environ. Res. 15: 206 (1978).
39. Kobayashi, J., Nakahara, H., and Hasegawa, T. Accumulation of cadmium in organs of mice fed on cadmium-polluted rice. Japan. J. Hyg. 26: 401 (1971).
40. Washko, P. W., and Cousins, R. J. Metabolism of ^{109}Cd in rats fed normal and low-calcium diets. J. Toxicol. Environ. Health 1: 1055 (1976).
41. Hamilton, D. L., and Smith, M. W. Inhibition of intestinal calcium uptake by cadmium and the effect of a low calcium diet on cadmium retention. Environ. Res. 15: 175 (1978).
42. Fowler, B. A., Jones, H. S., Brown, H. W., and Haseman,

J. K. The morphologic effects of chronic cadmium administration on the renal vasculature of rats given low and normal calcium diets. Toxicol. Appl. Pharmacol. 34: 233 (1975).

43. Itokawa, Y., Abe, T., Tabei, R., and Tanaka, S. Renal and skeletal lesions in experimental cadmium poisoning. Arch. Environ. Health 28: 149 (1974).

44. Itokawa, Y., Abe, T., and Tanaka, S. Bone changes in experimental chronic cadmium poisoning. Arch. Environ. Health 26: 241 (1973).

45. Cousins, R. J., and Feldman, S. L. Effect of cholecalciferol on cadmium uptake in the chick, Nutr. Rep. Int. 8: 363 (1973).

46. Suzuki, S., Taguchi, T., and Yokahashi, G. Dietary factors influencing upon the retention of orally administered $^{115m}CdCl_2$ in mice with special reference to calcium and protein concentrations in diet. Ind. Health 7: 155 (1969).

47. Muto, Y., and Omori, M. Nutritional influence on the onset of renal damage due to long-term administration of cadmium in young and adult rats. J. Nutr. Sci. Vitaminol. 23: 349 (1977).

48. Fox, M. R. S., Fry, B. E., Jr., Harland, B. F., Schertel, M. E., and Weeks, C. E. Effect of ascorbic acid on cadmium toxicity in the young coturnix. J. Nutr. 101: 1295 (1971).

49. Jacobs, R. M., Fox, M. R. S., Jones, A. O. L., Hamilton, R. P., and Lener, J. Cd metabolism: individual effects of Zn, Cu, and Mn. Fed. Proc. 36: 1152 (1977).

50. Banis, R. J., Pond, W. G., Walker, E. F., Jr., and O'Connor, J. R. Dietary cadmium, iron and zinc interactions in the growing rat. Proc. Soc. Exptl. Biol. Med. 130: 802 (1969).

51. Pond, W. G., and Walker, E. F., Jr. Cadmium induced anemia in growing rats: Prevention by oral or parenteral iron. Nutr. Rep. Int. 5: 365 (1972).

52. Pond, W. G., Walker, E. F., Jr., and Kirtland, D. Cadmium-induced anemia in growing pigs: protective effect of oral or parenteral iron. J. Anim. Sci. 36: 1122 (1973).

53. Webster, W. S. Cadmium-induced fetal growth retardation in the mouse. Arch. Environ. Health 33: 36 (1978).

54. Jacobs, R. M., Jones, A. O. L., Fox, M. R. S., and Fry, B. E., Jr. Retention of dietary cadmium and the ameliorative effect of zinc, copper, and manganese in Japanese quail. J. Nutr. 108: 22 (1978).

55. Jacobs, R. M., Jones, A. O. L., Fry, B. E., Jr., and Fox, M. R. S. Decreased long-term retention of ^{115m}Cd in Japanese quail produced by a combined supplement of zinc, copper and manganese. J. Nutr. 108: 901 (1978).

56. Fox, M. R. S., and Fry, B. E., Jr. Cadmium toxicity decreased by dietary ascorbic acid supplements. Science 169: 989 (1970).

57. Richardson, M. E., Fox, M. R. S., and Fry, B. E., Jr. Pathological changes produced in Japanese quail by ingestion of cadmium. J. Nutr. 104: 323 (1974).

58. Maji, T., and Yoshida, A. Therapeutic effect of dietary iron and ascorbic acid on cadmium toxicity of rats. Nutr. Rep. Int. 10: 139 (1974).

59. Stowe, H. D., Goyer, R. A., Medley, P., and Cates, M. Influence of dietary pyridoxine on cadmium toxicity in rats. Arch. Environ. Health 28: 209 (1974).

60. Fox, M. R. S., Jacobs, R. M., Fry, B. E., Jr., and Harland, B. F. Effect of protein source on response to cadmium. Fed. Proc. 32: 924 (1973).

61. Henke, G., Sachs, H. W., and Bohm, G. Cadmium-Bestimmungen in Leber und Nieren von Kindern und Jugendlichen durch Neutronenaktivierungsanalyse. Arch. Toxikol. 26: 8 (1970).

62. Kello, D., and Kostial, K. Influence of age and milk diet on cadmium absorption from the gut. Toxicol. Appl. Pharmacol. 40: 277 (1977).

63. Sasser, L. B., and Jarboe, G. E. Intestinal absorption and retention of cadmium in neonatal rat. Toxicol. Appl. Pharmacol. 41: 423 (1977).

64. Murata, I., Hirono, T., Saeki, Y., and Nakagawa, S. Cadmium enteropathy and renal osteomalacia ("Itai-itai" disease) in Japan. Bull. Soc. Int. Chir. 29: 34 (1969).

65. Yoshikawa, H., Hara, N., and Kawai, K. Experimental studies on cadmium stearate posioning. I. Dissociation curve and toxicity. Bull. Nat. Inst. Ind. Health 3: 61 (1960).

66. Wilson, R. H., DeEds, F., and Cox, W. H., Jr. Effects of continued cadmium feeding. J. Pharmacol. Exptl. Therap. 71: 222 (1941).

67. Stowe, H. D., Wilson, M., and Goyer, R. A. Clinical and morphologic effects of oral cadmium toxicity in rabbits. Arch. Pathol. 94: 389 (1972).

68. Richardson, M. E., and Fox, M. R. S. Dietary cadmium and enteropathy in the Japanese quail. Histochemical and ultrastructural studies. Lab. Invest. 31: 722 (1974).

69. Mason, K. E., Richardson, M. E., and Fox, M. R. S. Enteropathy caused by 1 or 10 ppm dietary Cd. Fed. Proc. 36: 1152 (1977).

70. Valberg, L. S., Haist, J., Cherian, M. G., Delaquernier-Richardson, L., and Goyer, R. A. Cadmium-induced enteropathy: comparative toxicity of cadmium chloride and cadmium-thionein. J. Toxicol. Environ. Health 2: 963 (1977).

71. Sugawara, C., and Sugawara, N. The effect of cadmium on soluble protein, enzymes, and essential metals of the duodenal mucosa. Arch. Environ. Contamin. Toxicol. 6: 121 (1977).

72. Fox, M. R. S., Hamilton, R. P., Jones, A. O. L., Fry, B. E., Jr., Jacobs, R. M., and Jones, J. W. Zinc and ascorbic acid antagonism of copper. Fed. Proc. 37: 324 (1978).

73. National Center for Health Statistics. Preliminary Findings of the First Health and Nutrition Examination Survey, U.S., 1971, 72. Anthropometric and Clinical Findings. DHEW Publication No. (HRA) 75-1229, Washington, D. C., 1975.

74. Abraham, S., et al. Dietary intake of persons 1-74 years of age in the United States. Advance Data, No. 6. National Center for Health Statistics, DHEW, Washington, D. C., 1977.

75. National Center for Health Statistics. Data from the National Health Survey. Dietary Intake Findings, United States, 1971-1974. DHEW Publication No. (HRA) 77-1647 Washington, D. C., 1977.

76. Hambidge, K. M., Hambidge, C., Jacobs, M., and Baum, J. D. Low levels of zinc in hair, anorexia, poor growth, and hypogeusia in children. Pediatr. Res. 6: 868 (1972).

77. Hambidge, K. M., and Silverman, A. Pica with rapid improvement after dietary zinc supplementation. Arch. Dis. Child. 48: 567 (1973).

78. Hambidge, K. M., Walravens, P. A., Brown, R. M., Webster, J., White, S., Anthony, M., and Roth, M. L. Zinc nutrition of preschool children in the Denver Head Start program. Amer. J. Clin. Nutr. 29: 734 (1976).

79. Harland, B., Prosky, L., and Vanderveen, J. Nutritional adequacy of current levels of Ca, Cu, Fe, I, Mg, Mn, P, Se and Zn in the American food supply for adults, infants and toddlers. In: Trace Element Metabolism in Man and Animals-3. M. Kirchgessner, Ed. Institut fur Ernahrungsphysiologie, Technische Universitat München, Freising-Weihenstephen, West Germany, 1978, p. 311.

80. White, H. S. Inorganic elements in weighed diets of girls and young women. J. Amer. Diet. Assoc. 55: 38 (1969).

81. Klevay, L. M. The ratio of zinc to copper of diets in the United States. Nutr. Rep. Int. 11: 237 (1975).

82. Gutherie, B. E., and Robinson, M. F. Daily intakes of manganese, copper, zinc and cadmium by New Zealand women. Brit. J. Nutr. 38: 55 (1977).

83. Wolf, W. R., Holden, J., and Greene, F. E. Daily intake of zinc and copper from self selected diets. Fed. Proc. 36: 1175 (1977).

84. Milne, D. B., Schnakenberg, D. D., and Johnson, H. L. Dietary intakes of copper, zinc, and manganese by military personnel. Fed. Proc. 37: 894 (1978).

85. Klevay, L. M. Dietary copper and the copper requirement of man. In: Trace Element Metabolism in Man and Animals-3. M. Kirchgessner, Ed., Institut fur Ernahrungsphysiologie, Technische Universitat München, Freising-Weihenstephen, West Germany, 1978, p. 307.

86. Fox, M. R. S. Nutritional considerations in designing animal models of metal toxicity in man. Environ. Health Perspect. 25: 137 (1978).